## REMARKS

With this Amendment, Applicants request continued examination with entry of a Supplemental Information Disclosure Statement and Amendment. Reconsideration of the rejection of all the claims is respectfully requested.

Claims 46 and 54 are canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

Claims 42, 47, 50, 55, 57, 58 and 61 are amended. Support for the amendments to claims can be found throughout the specification, including at Figure 2, Figure 4A-E, and supporting description at pages 9-10. Claim 61 is supported by the written description (e.g., on page 8, lines 9-12).

Applicants add new claims 66-69. New claims 66-67 are supported throughout the specification, including at page 8, lines 9-12, page 28 for claim 66 and pages 42-45 for claim 67. Claims 68 and 69 are supported throughout the specification, including at figure 2, page 9, lines 16-30, figures 4-4E and page 10, lines 4-9.

**Interview of January 27, 2004:**

The content of the discussion with Examiner Romeo of January 27, 2004 was reported by Gregory Zinkl and is included to comply with the requirement to record the substance of the interview.

The utility of the invention for diagnostic purposes was discussed with Examiner Romeo. Applicants noted that an antibody raised against a polypeptide of SEQ ID NO:3 is useful for detecting cancer. These antibodies are then useful in diagnostic arrays.

**35 U.S.C. § 101 and 35 U.S.C. § 112, ¶1 – Utility**

Claims 42-65 were rejected under 35 U.S.C. § 101 because the Examiner contends the present invention is not supported by a specific, a substantial asserted, or a well-established utility. Claims 42-65 were also rejected under 35 U.S.C. § 112, ¶1 because the Examiner contends that one of skill in the art would not know how to use the claimed invention due to the lack of utility under § 101. The Examiner alleges further research would be required to identify or reasonably confirm a "real world" context of use (i.e. substantial utility). Applicants respectfully traverse these rejections.

Applicants do not have to provide evidence sufficient to establish that an asserted utility is true beyond a reasonable doubt. *In re Irons*, 340 F.2d 974, 978 (CCPA 1965). Nor do Applicants have to provide evidence that establishes the asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-867 (CCPA 1980). Rather, Applicants only have the burden of presenting evidence that leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. MPEP § 2107.02 (emphasis in original).

The utility of the claimed invention is specific, substantial, and credible because the claimed invention is useful for many reasons including the detection of misregulation of the Wnt-1 pathway implicated in the transformation of cells into colon, breast, and ovarian cancers. The correlation between the source of SEQ ID NO:3 and the elevated expression of its human ortholog (SEQ ID NO:6) in human cancer cells demonstrates that SEQ ID NO:3 is useful for the detection of transformed cells. (See page 2, lines 14-20; and page 10, line 29 to page 11, line 11). Sufficient nexus is described between SEQ ID NO:3 to a correlated disease condition (i.e. cancer) to provide utility credible to one of skill in the art.

The Examiner asserts on pages 3 and 4 of the Office Action that in Table 8 the expression of SEQ ID NO:5 is unclear. [SEQ ID NO:5 is the human DNA ortholog to SEQ ID NO:2 which encodes for SEQ ID NO:3] The Examiner contends that one would not know whether the expression of SEQ ID NO:3 or SEQ ID NO:5 should be up-regulated, down-regulated, or unchanged in a particular cancer. Applicants disagree. In contrast to the Examiner's reading of Table 8, it is clear to one of skill in the art that SEQ ID NO:5 is over-expressed and therefore can be used to detect colon, breast and ovarian cancer as presented in Table 8.

Applicants also assert SEQ ID NO:3, the polypeptide of the claimed invention, can be used to detect the human sequences. The polypeptide of SEQ ID NO:3 can be used to generate antibodies, and those antibodies can be used to detect or treat cancers expressing human orthologs, such as SEQ ID NO:6. (See page 10, line 29 to page 11, line 11; page 31, line 17 to page 34, line 26; and page 56, line 14 to page 57, line 2). A "real world" use may be made of the antibody to probe biopsy samples or isolated cells from a subject, either human or mouse.

The polypeptide of SEQ ID NO:3 is also useful to test potential agents that can, for example, inhibit over-expression of SEQ ID NO:3 in an *in vitro* method or an animal model such as Wnt transgenic mice (p. 46, line 51 and page 68, lines 14-22). For example, the specification describes using animal models for atherosclerosis. See page 72, lines 22-30. Other animal

models involve examining the effect of agents that inhibit over-expression of SEQ ID NO:3 in animal models of graft vs. host or autoimmune disease. See page 76, line 16 to page 77, line 1. Finally, inhibitors may be tested in the Wnt transgenic mice as described in the examples. See page 87, line 30 to page 88, line 13.

The Examiner's assertion that SEQ ID NO:6 would be better suited for this utility or use is not relevant to the utility standard and analysis. The question is not whether SEQ ID NO:3 has inferior or superior utility, but rather does it have utility. The specification is sufficient such that a person skill in the art would conclude the polypeptide of SEQ ID NO:3 can be used successfully for the uses described above and therefore does possess utility.

In light of the specific, substantial and credible utility described above, Applicants respectfully request the rejections under 35 U.S.C. § 101 and related rejections under 35 U.S.C. § 112, ¶1 be withdrawn.

**35 U.S.C. § 112, ¶1 Written Description**

Claims 42-61 and 64 are rejected under 35 U.S.C. 112, ¶l for failing to comply with the written description requirement. The Examiner asserts that the claims are directed to a genus of amino acids having a percentage sequence identity with SEQ ID No:3 and that there is insufficient distinguishing characteristics to identify the genus. Applicants additionally traverse the Examiner's contention that "There is not even identification of any particular portion of the structure that must be conserved." Applicants respectfully traverse.

The written description requirement is satisfied when Applicants' specification conveys with reasonable clarity to those skilled in the art, that as of the filing date sought, he or she was in possession of the invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula ... of the claimed subject matter sufficient to distinguish it from other materials. Univ. of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (Fed. Cir. 1997) (emphasis added). Since one skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass, such a formula is normally an adequate description of the claimed invention. Id. at 1406 (emphasis added).

Moreover, as noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶1, "Written Description" Requirement ("the guidelines"), there is a "strong

presumption" that an adequate written description of the claimed invention is present when the application is filed, 66(4) Fed Reg. 1099, 1105 (2001); see also, In re Wertheim, 191 USPQ 90,97 (CCPA 1976). The guidelines further state that "[(The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) Fed. Reg. at 1107; 191 USPQ at 97, (emphasis added).

The claims are directed to a polypeptide comprising an amino acid sequence having a percentage of identity with SEQ ID NO:3. Additionally, the claims specify regions of SEQ ID NO:3 to be conserved in the calcium binding domain comprising amino acids 46-57, 59-61, 63, 65-70, and 72-85 ; comprising amino acids 46 through 85; or comprising amino acids 27-57, 59-61, 63, 65-70, 72- 99, 101-108, and 110-123. In the detailed description, the sequence and thereby the chemical structure of the polypeptide of SEQ ID NO:3 is provided. In addition, the relationship between the sequences, e.g, comparison between SEQ ID NO:3 and SEQ ID NO:6 is shown in figure 2 and described in the detailed description at page 9, lines 16-30. In figure 2, the regions of identity are identified in the darkened blocks supporting the conclusion that the sequences are orthologs and provide further structural information regarding regions of amino acid conservation.

Additional structural comparisons are made between SEQ ID NO:3 and its human ortholog SEQ ID NO:6 in FIGS 4A through 4E, which illustrate the significant homology between SEQ ID NO:3, SEQ ID NO:6 and other members of the S100 cytokine family. Figure 4A is a BLOCKS protein domain analysis of the polypeptide of SEQ ID NO:6 with other calcium binding proteins (SEQ ID NOs:12-36) which shows the two conserved calcium binding regions separated by 8 amino acids, which is characteristic of S100 proteins. (Page 9, line 28-30). Figure 4B shows an alignment of the amino acids 28-131 of SEQ ID NO:3 with amino acids 1-101 of Acc. No. AY007220 (SEQ ID NO:39), an S100 type calcium binding protein and the resulting consensus sequence (SEQ ID NO:40). Figure 4D shows an alignment of calcium binding domains including amino acids 46 to 85 of SEQ ID NO:3 with various calcium binding proteins.

In these figures, identical or conserved amino acids residues are indicated in black shading. As directed by the specification, amino acids shaded in grey can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or

function. Non-highlighted amino acid residues can potentially be mutated to a much broader extent without altering structure or function. (Page 10, lines 4-9). The claims, as amended, define the claimed genus as related to SEQ ID NO:3. The above described comparisons, additionally supported by guidance on sequence identity on page 16, lines 5-15 and discussion of variants at pages 17-21 provides more than adequate guidance to one of skill in the art to recognize the claimed invention from Applicant's disclosure and sufficient recitation of distinguishing identifying characteristics to define the claimed genus.

Claim 61 is amended from a dependent claim to an independent claim. By amending claim 61, Applicants do not acquiesce to the rejection. Claim 61, as amended, is directed to the a polypeptide consisting of SEQ ID NO:3. Therefore, rejection under § 112, first paragraph, on the basis of percentage sequence identity is inapplicable.

The Examiner asserts that the lack of an N-terminal Methionine renders the scope of the claims to be unclear. Applicants respectfully traverse. Claims are to be interpreted in light of the specification. The claims require sequence identity to SEQ ID NO:3 which is explicitly defined in the detailed description. Guidance on determining sequence identity is provided on page 27, line 4 to page 28, line 2 which indicates the percentage of sequence identity is calculated to a "region of comparison", in this case a region corresponding to SEQ ID NO:3. Additional sequence is not required by the claims, the scope of which is not unclear.

In light of the above comments, Applicants respectfully request withdrawal of the rejection of the claims under the written description requirement.

**35 U.S.C. § 112, ¶1 Enablement**

Claims 42-61 and 64 are rejected under 35 U.S.C. 112, ¶1 for failing to comply with the enablement requirement. Claims 42-60 and 64 are directed to a polypeptide comprising an amino acid sequence 90, 95, or 99% identical to SEQ ID NO:3 and The examiner contends the claims are non-enabling because the claims encompass an unreasonable number of inoperative polypeptides, which a skilled artisan would not know how to use. Claim 61 is directed to a polypeptide consisting of an amino acid sequence of SEQ ID NO:3. Applicants respectfully traverse.

The arguments presented above in support of utility and written description of the invention also support the subject matter of the claims being described in the specification in a

way to enable one of skill in the art to make and use the invention. Those arguments are incorporated here without restatement.

The legal standard for enablement under 35 U.S.C. § 112 requires that "[...] a patent specification must disclose sufficient information to enable **those skilled in the art** to make the claimed invention." *Hormone Research Foundation, Inc. v. Genentech*, 15 USPQ2d 1039, 1047 (Fed. Cir. 1990). It is a well accepted premise that §112¶1 requires only that a patent specification describe to one of ordinary skill in the art how to make and use the claimed invention without **undue** experimentation. Under the law of enablement, a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as satisfying the enablement requirement unless there is reason to doubt the objective truth of the specification. In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971). It is incumbent upon the Examiner to explain why one skilled in the art would doubt the truth of statements made in the specification, and provide back up assertions with acceptable evidence or reasoning which is inconsistent with the teachings of the specification. Id. at 370. Absent evidence to the contrary, the specification must be assumed to be enabling.

Sufficient recitation of distinguishing identifying characteristics is present in claims 42-60 and 64 to identify the claimed genus and the specification provides information sufficient to enable one of skill in the art to make and use the claimed invention. Structural information, as well as, multiple comparisons to the human ortholog (SEQ ID NO:6) and S100 family members are provided in Figures 1-4E. In these figures, identical or conserved amino acids residues are indicated in black shading. (Page 10, lines 4-5). The specification indicates that amino acids shaded in grey can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or function. (Page 10, lines 6-7). The specification further directs that non-highlighted amino acid residues can potentially be mutated to a much broader extent without altering structure or function. (Page 10, lines 8-9).

The above described comparisons, additionally supported by guidance on sequence identity on page 16, lines 5-15 and discussion of variants at pages 17-21 provides more than adequate guidance to one of skill in the art to make and use the claimed invention without undue experimentation. Examiner's assertion of an unreasonable number of inoperative polypeptides is unsupported and untenable in light of the evidence presented and the legal standard. Withdrawal of the enablement rejection is respectfully requested.

**35 U.S.C. § 112, ¶2 Indefiniteness**

Claims 42-47 were rejected under 35 U.S.C. §112 ¶2 for use of the phrase "selectively binds". By amending the claims, Applicants do not acquiesce to the rejection. The language requiring antibody binding has been removed thereby rendering the rejection on the basis of indefiniteness moot. Withdrawal of the indefiniteness rejection is respectfully requested.

**35 U.S.C. § 102e**

Claims 46, 47, 49, 54, 55 and 57 were rejected under 35 U.S.C. 102(e) as being anticipated by Bandman, U.S. Patent No. 6,117,989 (hereinafter Bandman). Solely to expedite prosecution and without acquiescing to the Examiner's rejection, Applicants have canceled claims 46 and 57, and amended claimed 47, 49, 55 and 57 to no longer depend on claims 46 and 54. Cancelled independent claims 46 and 54 were directed to a "fragment having at least 10 amino acids". Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications. Applicants submit that the claims as amended render the rejection moot and respectfully request withdrawal of the rejection.

**Summary**

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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July 6, 2004
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